REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

I. CLAIM STATUS AND AMENDMENTS

Claims 1-13 were pending in this application when last examined and stand rejected.

Claim 1 is amended to incorporate the subject matter of claim 7.

Claim 12 is amended to specify a "method for prepaing medicinal products. . . " as suggested by the Office. Support 12 can be found in the claim as filed.

Claims 1-6 and 8-13 have also been amended to improve the language to better conform to U.S. practice and English grammar form. These revisions are non-substantive and not intended to narrow the scope of protection. Support can be found in the claims as filed.

No new matter has been added by the above claim amendments.

Claim 7 has been canceled without prejudice or disclaimer thereto. Applicants reserve the right to file a continuation or divisional application on any canceled subject matter.

New claims 14-15 have been added.

Support for new claim 14 can be found in the disclosure, for example, at page 7, lines 4-9.

Support for new claim 15 can be found in the disclosure, for example, at page 12, lines 10-20.

Claims 1-6 and 8-15 are pending upon entry of this amendment.

The specification is amended at page 5, line 22 on, to include a BRIEF SUMMARY OF THE INVENTION section as supported by the claims as filed. The specification is also amended at page 5, line 22 on, to include a BRIEF DESCRIPTION OF THE DRAWINGS as supported by the disclosure, for example, at page 9, lines 9-11, lines 16 to page 10, line 7, and page 11, line 19, to page 12, line 4. No new matter has been added by such amendments.

II. OBJECTION TO SPECIFICATION

On page 3 of the Office Action, the specification was objected to for containing minor informalities.

It is respectfully submitted that the present amendment overcomes this objection. It is noted that the specification has been amended along the lines suggested by the Office. Therefore, withdrawal of the objection is solicited.

III. CLAIM OBJECTION

On page 3 of the Office Action, claim 12 was objected to for containing minor informalities.

It is respectfully submitted the present amendment overcomes this objection. Claim 12 has been amended along the lines suggested by the Office to specify a "method for preparing medicinal products . . ." Withdrawal of the objection is therefore solicited.

IV. OBVIOUSNESS REJECTIONS

On page 4 of the Office Action, claims 1-4, 7-9 and 11-13 were rejected under 35 USC §103(a) as allegedly obvious over FRIEDMAN et al. in view of RILEY.

On page 8 of the Office Action, claim 10 was rejected under 35 USC §103(a) as obvious over FRIEDMAN et al. in view of RILEY and further in view of SMOLINSKE.

On page 9 of the Office Action, claims 5 and 6 were rejected under 35 USC §103(a) as obvious over FRIEDMAN et al. in view of RILEY and further in view of BONDA.

These rejections are respectfully traversed as applied to the amended claims. These rejections will be addressed together below, given that FRIEDMAN et al. is the primary reference used throughout.

Applicants respectfully traverse these rejections as applied to the amended claims and new claims.

The present amendment incorporates claim 7 into independent claim 1. By this amendment, the amended claims call for sodium hyaluronate in the water-in-oil microemulsion. As

discussed at page 5, line 19, of the instant disclosure, the Applicants have found that retinoids can be advantageously formulated in water-in-oil microemulsions using a phospholipid emulsifier and hyaluronic acids. It is noted that the use of sodium hyaluronate in the present invention promotes percutaneous absorption. See, for instance, page 6, lines 5-6.

FRIEDMAN fails to disclose or suggest water-in-oil microemulsions containing retinoids, a phospholipid emulsifier and sodium hyaluronate with such properties. In fact, as acknowledged at the top page 6 of the Office Action, "Friedman et al. does not disclose a water-in-oil microemulsion."

Nonetheless, even if FRIEDMAN discloses oil-in-water emulsions similar to the water-in-oil emulsions of the present application in terms of amounts and type of ingredients, such emulsions contain hyaluronic acid as a mucoadhesive polymer, because they are intended for administering a drug on a mucosal surface. See, for example, claim 1 of FRIEDMAN. FRIEDMAN never mentions the use of sodium hyaluronate in a water-in-oil microemulsion to promote percutaneous absorption.

Further, it is noted that in the water-in-oil microemulsions of the present invention, hyaluronic acid is necessary in order to increase the bioavailability of the active principle by increasing percutaneous absorption. See, for instance, page 12, table and lines 18-22, of the instant disclosure.

In the present invention, it is also pointed out that hyaluronic acid has a viscosizing effect and that the emulsions are preferably applied to skin for treating hyperproliferative diseases, such as acne, psoriasis and lichen planus.

The primary reference of FRIEDMAN fails to disclose or suggest water-in-oil microemulsions with such properties. In fact, none of the cited references, including the secondary references of RILEY, SMOLINSKE and BONDA, disclose or suggest such properties of the present invention.

RILEY is concerned with controlled-release bioadhesive systems whose properties vary along with temperature. In RILEY, the systems are solid at room temperature and melt at body temperature (see, column 1, lines 56-57 and column 4, line 43) and they are intended mainly for rectal administration. Thus, the systems of RILEY are not thermally stable as in the present invention. One of the main features of the water-in-oil microemulsions of the present invention is thermal stability.

SMOLINSKE relates to a discussion of the use of parabens in drugs and cosmetics. It does not disclose or suggest their use in water-in-oil microemulsions as in the present invention.

BONDA discusses the use of retinoids. BONDA also discloses how to solubilize and stabilize isoretinoin by means of naphthalene derivatives. However, BONDA does not teach or suggest the use hyalurnoic acid for stabilizing water-in-oil

microemulsions containing retinoids, according to the present invention.

Therefore, it is respectfully submitted that none of the cited references disclose or suggest the claimed water-in-oil microemulsions containing retinoids, a phospholipid emulsifier and sodium hyaluronate with such improved properties.

Furthermore, it is well established that obviousness requires a reasonable expectation of success, which means that the combination of cited references would have yielded nothing more than predictable results to one of ordinary skill in the art. *See, KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1395 (2007); and M.P.E.P. § 2143.02.

In this respect, the Office, at page 6 of the Official Action, states that "Friedman et al. cites Riley Jr., US Patent 5,055,303, as prior art disclosing bioadherent emulsions of the water-in-oil type (column 2, lines 35-40)" and "one of ordinary skill in the art at the time of the invention would have been motivated to use the prior art technique of a bioadherent emulsion of the water-in-oil type to improve the emulsions with bioadherent properties of FRIEDMAN."

Applicants respectfully disagree and submit that the combined the cited references would not have yielded predictable results to arrive at the claimed water-in-oil microemulsions containing retinoids, a phospholipid emulsifier and sodium hyaluronate with such properties as in claim 1. In this regard,

Applicants would like to point out that there is a clear structural difference between "emulsions" as used in FRIEDMAN and RILEY and "microemulsions" of the claim 1, which goes beyond particle size. As is clear from the definitions reported in the Wikipedia (which is deemed to be common general knowledge), an ewulsion is a mixture of two immiscible substances (see enclosure 1). Emulsions tend to have a cloudy appearance, are unstable and tend to revert to the stable state of oil separated from water. Instead, microemulsions (see enclosure 2) are stable ternary systems made of an oily phase, water and a surfactant and are thermal dynamically stable.

Based on such understanding, Applicants submit that the use of microemulsions rather than emsulsions (as done in the cited references) would not constitute a mere substitution of one known element for another to obtain predictable results. This is further evident in the superiority of microemulsions over emulsions as demonstrated in the instant application.

See, for instance, the description and working examples on pages 10-12 of the specification, including, Example 5. As shown in Figure 4, the water-in-oil microemulsions of the present invention using sodium hyaluronate show surprisingly improved performance over those without sodium hyaluronate and those carried in conventional formulations. More specifically, in Figure 4, gel microemulsions containing fenretinide are compared to conventional formulations containing fenretinide. It is

pointed out that the ointment base containing cetomacrogol and the fatty cream base containing cetomacrogol are not microemulsions, in particular, the cream is a hydrophilic emulsion, since cetomacrogol is an emulsifying agent. Enclosure 3 is an excerpt from the European pharmacopoeia reporting the definition of creams, while Enclosure 4 is an excerpt from the Handbook of Pharmaceutical Excipients, 3rd ed., showing that cetomacrogol, which is a polyoxyethylene alkyl ether, can be used as an emulsifying agent. Thus, Figure 4 shows that microemulsions containing fenretinide have higher absorption rate than conventional emulsions.

See, also the discussion in the bottom half of page 12 (and Figure 6), wherein it is demonstrated that the claimed invention achieves surprisingly greater diffusion and permeation (absorption rate) of fenretinide to therefore promote percuntaneous absorption. As such, Figure 6 demonstrates that microemulsions according to present claim 1, *i.e.*, water-in-oil microemulsions containing sodium hyaluronate, have higher absorption rates than microemulsions not containing it. As a result, the present invention provides better bioavailability than the conventional formulations in the cited references.

Such an improvement in the absorption rate by using the system of claim 1 could not have been predicted on the basis of the information contained in the cited art references and known differences between emulsions and microemulsions as discussed

above. Thus, it is respectfully submitted that such properties amount to surprising and unexpected results over the cited art references.

Therefore, it is respectfully submitted that a skilled person, upon reading the references and in view of the state of the art, would not have applied the teaching of RILEY (*i.e.*, water-in-oil microemulsions) to FRIEDMAN in order to obtain stable systems of water-in-oil microemulsions containing retinoids, a phospholipid emulsifier and sodium hyaluronate with such improved properties suitable for application to skin.

As for claim 8, Applicants respectfully submit that the rejection is improper in view of the amended claims replacing the term "salified" with "HA salts". As such, the claim is no longer a product-by-process claim.

For these reasons, it is the amended claims are novel and unobvious over the combination of cited references. Therefore, it is respectfully submitted that the above-noted §103 obviousness rejections are untenable and should be withdrawn.

V. CONCLUSION

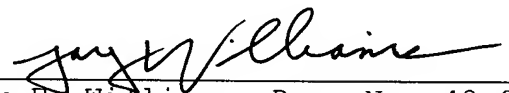
In view of the foregoing amendments and remarks, it is respectfully requested that the present application is in condition for allowance and an early notice to that effect is hereby requested.

If the Examiner has any comments or proposals for expediting prosecution, please contact the undersigned attorney at the telephone number below.

The Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

YOUNG & THOMPSON



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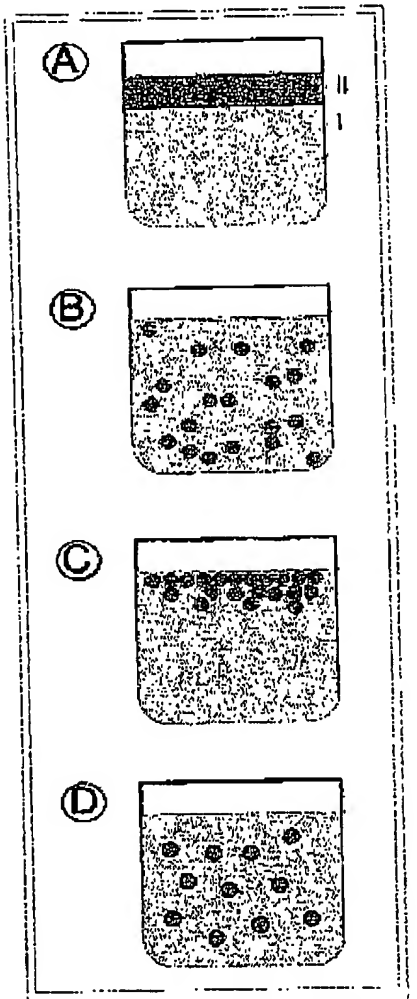
ENCLOSURE 1

Emulsion

From Wikipedia, the free encyclopedia

An **emulsion** (IPA: /ɪˈmʌlʃən/[1]) is a mixture of two immiscible (unblendable) substances. One substance (the dispersed phase) is dispersed in the other (the continuous phase). Examples of emulsions include butter and margarine, milk and cream, espresso, mayonnaise, the photo-sensitive side of photographic film, magmas and cutting fluid for metal working. In butter and margarine, a continuous liquid phase surrounds droplets of water (a water-in-oil emulsion). In milk and cream, oil is dispersed within a continuous water phase (an oil-in-water emulsion). In certain types of magma, globules of liquid NiFe may be dispersed within a continuous phase of liquid silicates. Emulsification is the process by which emulsions are prepared.



A. Two immiscible liquids, not emulsified; B. An emulsion of Phase II dispersed in Phase I; C. The unstable emulsion progressively separates; D. The surfactant (purple outline) positions itself on the interfaces between Phase II and Phase I, stabilizing the emulsion

Emulsions tend to have a cloudy appearance, because the many phase interfaces (the boundary between the phases is called the interface) scatter light that passes through the emulsion. Emulsions are unstable and thus do not form spontaneously. Energy input through shaking, stirring, homogenizers, or spray processes are needed to form an emulsion. Over time, emulsions tend to revert to the stable state of oil separated from water. Surface active substances (surfactants) can increase the kinetic stability of emulsions greatly so that, once formed, the emulsion does not change significantly over years of storage. Homemade oil and vinegar salad dressing is an example of an unstable emulsion that will quickly separate unless shaken continuously. This phenomenon is called coalescence, and happens when small droplets recombine to form bigger ones. Fluid emulsions can also suffer from creaming, the migration of one of the substances to the top of the emulsion under the influence of buoyancy or centripetal force when a centrifuge is used.

Emulsions are part of a more general class of two-phase systems of matter called colloids. Although the terms colloid and emulsion are sometimes used interchangeably, emulsion tends to imply that both the dispersed and the continuous phase are liquid.

There are three types of emulsion instability: flocculation, where the particles form clumps; creaming, where the particles concentrate towards the surface (or bottom, depending on the relative density of the two phases) of the mixture while staying separated; and breaking and coalescence where the particles coalesce and form a layer of liquid.

Emulsion is also a term used in the oil field as untreated well production that consists primarily of crude oil and water.

ENCLOSURE 2

Microemulsion

From Wikipedia, the free encyclopedia

Microemulsions are clear, stable, isotropic liquid mixtures of oil, water and surfactant, frequently in combination with a cosurfactant. The aqueous phase may contain salt(s) and/or other ingredients, and the "oil" may actually be a complex mixture of different hydrocarbons and olefins. In contrast to ordinary emulsions, microemulsions form upon simple mixing of the components and do not require the high shear conditions generally used in the formation of ordinary emulsions. The two basic types of microemulsions are direct (oil dispersed in water, o/w) and reversed (water dispersed in oil, w/o).

In ternary systems such as microemulsions, where two immiscible phases (water and 'oil') are present with a surfactant, the surfactant molecules may form a monolayer at the interface between the oil and water, with the hydrophobic tails of the surfactant molecules dissolved in the oil phase and the hydrophilic head groups in the aqueous phase. As in the binary systems (water/surfactant or oil/surfactant), self-assembled structures of different types can be formed, ranging, for example, from (inverted) spherical and cylindrical micelles to lamellar phases and bicontinuous microemulsions, which may coexist with predominantly oil or aqueous phases.

Contents

Uses

Microemulsions have many commercially important uses. The fluid used in some dry cleaning processes is a water-in-oil microemulsion. Some floor polishes and cleaners, personal care products, pesticide formulations, and cutting oils are actually microemulsions. Much of the work done on these systems have been motivated by their possible use to mobilize petroleum trapped in porous sandstone for enhanced oil recovery. A fundamental reason for the uses of these systems is that a microemulsion phase sometimes has an ultralow interfacial tension with a separate oil or aqueous phase, which may release or mobilize them from solid phases even in conditions of slow flow or low pressure gradients.

Theory

Various theories concerning microemulsion formation, stability and phase behavior have been proposed over the years. For example, one explanation for their thermodynamic stability is that the oil/water dispersion is stabilized by the surfactant present and their formation involves the elastic properties of the surfactant film at the oil/water interface, which involves as parameters, the curvature and the rigidity of the film. These parameters may have an assumed or measured pressure and/or temperature dependence (and/or the salinity of the aqueous phase), which may be used to infer the region of stability of the microemulsion, or to delineate the region where three coexisting phases occur, for example. Calculations of the interfacial tension of the microemulsion with a coexisting oil or aqueous phase are also often of special focus and may sometimes be used to guide

ENCLOSURE 3

Creams

DEFINITION

Creams are multiphase preparations consisting of a lipophilic phase and an aqueous phase.

Lipophilic Creams

Lipophilic creams have as the continuous phase the lipophilic phase. They contain water-in-oil emulsifying agents such as wool alcohols, sorbitan esters and monoglycerides.

Hydrophilic Creams

Hydrophilic creams have as the continuous phase the aqueous phase. They contain oil-in-water emulsifying agents such as sodium or trolamine soaps, sulphated fatty alcohols, polysorbates and polyoxyl fatty acid and fatty alcohol esters combined, if necessary, with water-in-oil emulsifying agents.

Gels

DEFINITION

Gels consist of liquids gelled by means of suitable gelling agents.

Lipophilic Gels

Lipophilic gels (oleogels) are preparations whose bases usually consist of liquid paraffin with polyethylene or fatty oils gelled with colloidal silica or aluminium or zinc soaps.

Hydrophilic Gels

Hydrophilic gels (hydrogels) are preparations whose bases usually consist of water, glycerol or propylene glycol gelled with suitable gelling agents such as starch, cellulose derivatives, carbomers and magnesium-aluminium silicates.

Pastes

DEFINITION

Pastes are semi-solid preparations for cutaneous application containing large proportions of solids finely dispersed in the basis.

Poultices

DEFINITION

Poultices consist of a hydrophilic heat-retentive basis in which solid or liquid active substances are dispersed. They are usually spread thickly on a suitable dressing and heated before application to the skin.

Medicated plasters

DEFINITION

Medicated plasters are flexible preparations containing one or more active substances. They are intended to be applied to the skin. They are designed to maintain the active substance(s) in close contact with the skin such that these may be absorbed slowly, or act as protective or keratolytic agents.

Medicated plasters consist of an adhesive basis, which may be coloured, containing one or more active substances, spread as a uniform layer on an appropriate support made of natural or synthetic material. It is not irritant or sensitising to the skin. The adhesive layer is covered by a suitable protective liner, which is removed before applying the plaste, to the skin. When removed. the protective liner does not detach the preparation from the outer, supporting layer.

Medicated plasters are presented in a range of sizes directly adapted to their intended use or as larger sheets to be cut before use. Medicated plasters adhere firmly to the skin when gentle pressure is applied and can be peeled off without causing appreciable injury to the skin or detachment of the preparation from the outer, supporting layer.

TESTS

Dissolution. A suitable test may be required to demonstrate the appropriate release of the active substance(s), for example one of the tests described in *Dissolution test for transdermal patches* (*2.9.4*).

01/2002:1154

STICKS

Styli

Additional requirements for sticks may be found, where appropriate, in other general monographs, for example Nasal preparations (0676).

DEFINITION

Sticks are solid preparations intended for local application. They are rod-shaped or conical preparations consisting of one or more active substances alone or which are dissolved or dispersed in a suitable basis which may dissolve or melt at body temperature.

Urethral sticks and sticks for insertion into wounds are sterile.

PRODUCTION

In the manufacture, packaging, storage and distribution of sticks, suitable means are taken to ensure their microbial quality; recommendations on this aspect are provided in the text on *Microbiological quality of pharmaceutical preparations* (*5.1.4*).

Urethral sticks and other sterile sticks are prepared using materials and methods designed to ensure sterility and to avoid the introduction of contaminants and the growth of micro-organisms; recommendations on this aspect are provided in the text on *Methods of preparation of sterile products* (*5.1.1*).

In the manufacture of sticks means are taken to ensure that the preparation complies with a test for mass uniformity or, where appropriate, a test for uniformity of content.

TESTS

Sterility (*2.6.1*). Urethral sticks and sticks for insertion into wounds comply with the test for sterility.

LABELLING

The label states:

- the quantity of active substance(s) per stick,
- for urethral sticks and sticks to be inserted into wounds that they are sterile.

ENCLOSURE 1

Handbook of PHARMACEUTICAL EXCIPIENTS

Third Edition

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Polyoxyethylene Alkyl Ethers

1. Nonproprietary Names

The polyoxyethylene alkyl ethers are a series of polyoxyethylene glycol ethers of *n*-alcohols (lauryl, myristyl, cetyl, and stearyl alcohol). Of the large number of different materials commercially available, two types are listed in the USP, one type in the BP, one type in the JP, and three types in the PhEur.

BP: Cetomacrogol 1000
JP: Lauromacrogol 400
PhEur: Macrogoli aethurum cetostearylicum
PhEur: Macrogoli aethurum laurilicum
PhEur: Macrogoli aethurum oleicum
USP: Polyoxyl 20 cetostearyl ether
USP: Polyoxyl 10 oleyl ether

Polyoxyethylene alkyl ethers are extensively employed in cosmetics where the CTFA names laureth-N, myreth-N, ceteth-N, and steareth-N are commonly used. In this nomenclature, N is the number of ethylene oxide groups, e.g., steareth-20.

See also Sections 2-5, and 17.

2. Synonyms

Polyoxyethylene alkyl ethers are nonionic surfactants produced by the polyethoxylation of linear fatty alcohols. Products tend to be mixtures of polymers of slightly varying molecular weights and the numbers used to describe polymer lengths are average values.

Two systems of nomenclature are used to describe these materials. The number '10' in the name '*Texofor A10*' refers to the approximate polymer length in oxyethylene units (i.e. *y*, *see* Section 5). The number '1000' in the name 'cetomacrogol 1000' refers to the average molecular weight of the polymer chain.

Synonyms applicable to polyoxyethylene alkyl ethers are shown below:

Brij; *Cremophor A*; *Cyclogol 1000*; *Empilan KB*; *Empilan KM*; *Ethylan C*; macrogol ethers; *Marlowet*; *Plurafac*; *Procol*; *Texofor A*; *Volpo*.

Table I shows synonyms for specific materials.

Table I: Synonyms of selected polyoxyethylene alkyl ethers.

Name	Synonym
Cetomacrogol 1000	Polyethylene glycol 1000; macrocetyl ether; polyoxyethylene glycol 1000; monocetyl ether.
Polyoxyl 20 cetostearyl ether	*Atlas G-3713*.
Polyoxyl 2 cetyl ether	*Brij 52*; ceteth-2.
Polyoxyl 10 cetyl ether	*Brij 56*; ceteth-10.
Polyoxyl 20 cetyl ether	*Brij 58*; ceteth-20.
Polyoxyl 4 lauryl ether	*Brij 30*; laureth-4.
Polyoxyl 9 lauryl ether	Lauromacrogol 400; laureth 9; polidocanol.
Polyoxyl 23 lauryl ether	*Brij 35*; laureth-23.
Polyoxyl 2 oleyl ether	*Brij 92*; *Brij 93*; oleth-2.
Polyoxyl 10 oleyl ether	*Brij 96*; *Brij 97*; oleth-10; polyethylene glycol monooleyl ether; *Volpo 10*.
Polyoxyl 20 oleyl ether	*Brij 98*; *Brij 99*; oleth-20; *Volpo 20*.
Polyoxyl 2 stearyl ether	*Brij 72*; steareth-2; *Volpo S-2*.
Polyoxyl 10 stearyl ether	*Brij 76*; steareth-10; *Volpo S-10*.
Polyoxyl 20 stearyl ether	*Brij 78*; steareth-20; *Volpo S-20*.
Polyoxyl 100 stearyl ether	*Brij 700*; steareth-100.

3. Chemical Name and CAS Registry Number

Polyethylene glycol monocetyl ether [9004-95-9]
Polyethylene glycol monolauryl ether [9002-92-0]
Polyethylene glycol monooleyl ether [9004-98-2]
Polyethylene glycol monostearyl ether [9005-00-9]

4. Empirical Formula Molecular Weight

See Sections 1, 2, and 5.

5. Structural Formula

$CH_3(CH_2)_x(OCH_2CH_2)_yOH$

Where $(x + 1)$ is the number of carbon atoms in the alkyl chain, typically:

12 lauryl (dodecyl)
14 myristyl (tetradecyl)
16 cetyl (hexadecyl)
18 stearyl (octadecyl)

and y is the number of ethylene oxide groups in the hydrophilic chain, typically 10-60.

The polyoxyethylene alkyl ethers tend to be mixtures of polymers of slightly varying molecular weights, and the numbers quoted are average values. In cetomacrogol 1000, for example, x is 15 or 17, and y is 20-24.

6. Functional Category

Emulsifying agent; solubilizing agent; wetting agent.

7. Applications in Pharmaceutical Formulation or Technology

Polyoxyethylene alkyl ethers are nonionic surfactants widely used in topical pharmaceutical formulations and cosmetics primarily as emulsifying agents for water-in-oil and oil-in-water emulsions.

Polyoxyethylene alkyl ethers are also used in other applications such as: solubilizing agents for essential oils, perfumery chemicals, vitamin oils, and drugs of low-water solubility; gelling and foaming agents, e.g., *Brij 72* gives a quick-breaking foam, while *Brij 97* (and others) gives clear gels at 15-20% concentration; antidusting agents for powders; wetting and dispersing agents for coarse-particle liquid dispersions; and detergents, especially in shampoos and similar cosmetic cleaning preparations.

8. Description

Polyoxyethylene alkyl ethers vary considerably in their physical appearance from liquids, to pastes, to solid waxy substances. They are colorless, white or cream-colored materials with a slight odor.

9. Pharmacopeial Specifications

Test	BP Cetomacrogol 1000	JP Lauromacrogol	USP Polyoxyl 20 cetostearyl ether	USP Polyoxyl 10 oleyl ether
Identification	+	+	+	+
Characters	+	+	—	—
Water	≤ 1.0%	—	≤ 1.0%	≤ 3.0%
pH (10% solution)	—	—	4.5-7.5	—
Alkalinity	+	—	—	—
Acidity	—	+	—	—
Melting point	≥ 38°C	—	—	—
Refractive index at 60°C	1.448-1.452	—	—	—
Residue on ignition	—	≤ 0.20%	≤ 0.4%	≤ 0.4%
Heavy metals	—	—	≤ 0.002%	≤ 0.002%
Acid value	≤ 0.5	—	≤ 0.5	≤ 1.0
Hydroxyl value	40.0-52.5	—	42-60	75-95
Iodine value	—	—	—	23-40
Saponification value	≤ 1.0	—	≤ 2	≤ 3
Free polyethylene glycols	—	—	≤ 7.5%	≤ 7.5%
Free ethylene oxide	—	—	≤ 0.01%	≤ 0.01%
Average polymer length	—	—	17.2-25.0	8.6-10.4
Organic volatile impurities	—	—	+	—
Trichloroethylene	—	—	≤ 100 ppm	—

10. Typical Properties

See Tables II and III.

11. Stability and Storage Conditions

Polyoxyethylene alkyl ethers are chemically stable in strongly acidic or alkaline conditions. The presence of strong electrolytes may however adversely affect the physical stability of emulsions containing polyoxyethylene alkyl ethers.

On storage, polyoxyethylene alkyl ethers can undergo autoxidation, resulting in the formation of peroxides with an increase in acidity. Many commercially available grades are thus supplied with added antioxidants. Typically, a mixture of 0.01% butylated hydroxyanisole and 0.005% citric acid is used for this purpose.

Polyoxyethylene alkyl ethers should be stored in an airtight container, in a cool, dry, place.

12. Incompatibilities

Discoloration and/or precipitation occurs with iodides, mercury salts, phenolic substances, salicylates, sulfonamides, and tannins. Polyoxyethylene alkyl ethers are also incompatible with benzocaine and oxidizable drugs.[1]

The antimicrobial efficacy of some phenolic preservatives, such as the parabens, is reduced due to hydrogen bonding. Cloud points are similarly depressed by phenols due to hydrogen bonding between ether oxygen atoms and phenolic hydroxyl groups. Salts, other than nitrates, iodides, and thiocyanates (which cause an increase) can also depress cloud points.[2]

13. Method of Manufacture

Polyoxyethylene alkyl ethers are prepared by the condensation of linear fatty alcohols with ethylene oxide. The reaction is controlled so that the required ether is formed with the polyethylene glycol of the desired molecular weight.

14. Safety

Polyoxyethylene alkyl ethers are used as nonionic surfactants in a variety of topical pharmaceutical formulations and cosmetics. The polyoxyethylene alkyl ethers form a series of materials with varying physical properties and manufacturers' literature should be consulted for information on the applications and safety of specific materials.

Although generally regarded as essentially nontoxic and nonirritant materials some polyoxyethylene alkyl ethers, particularly when used in high concentration (> 20%), appear to have a greater irritant potential than others.

Animal toxicity studies suggest that polyoxyethylene alkyl ethers have a similar oral toxicity to other surfactants and can be regarded as being moderately toxic. In rats, the oral LD_{50} values range from about 2-4 g/kg body-weight.

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended.

16. Regulatory Status

Included in nonparenteral medicines licensed in the US and UK.

17. Pharmacopeias

Name	Pharmacopeia
Cetomacrogol 1000	Br and Int
Macrogol cetostearyl ether	Eur
Macrogol lauryl ether	Eur
Macrogol oleyl ether	Eur
Polyoxyl 20 cetostearyl ether	US
Polyoxyl 10 oleyl ether	US

18. Related Substances

Nonionic emulsifying wax.

Many other polyoxyethylene ethers, such as diethers and polyethers, are commercially available and are also used as surfactants. In addition to their surfactant properties, the series of polyoxyethylene ethers with alky lauryl side chains, e.g., nonoxynol 10, are also widely used as spermicides.

19. Comments

Table 6: Typical properties of selected commercial [illegible]

Name	Physical form	Acid value	HLB value	Hydroxyl value	Iodine number	Saponification value	Density g/cm³ at 20°C	Water content (%)	Melting point or pour point (°C)	Cloud point (°C) for 1% aqueous solution
Brij 30	Liquid	≤ 2	9.7	145-165	—	—	≈ 0.95	≤ 1.0	—	—
Brij 35	Solid	≤ 5	16.9	40-60	—	—	≈ 1.05	≤ 3.0	33	—
Brij 52	Solid	≤ 1	5.3	160-180	—	—	—	≤ 1.0	33	—
Brij 56	Solid	≤ 1	12.9	75-90	—	—	—	≤ 3.0	31	—
Brij 58	Solid	≤ 1	15.7	45-60	—	—	—	≤ 3.0	38	—
Brij 72	Solid	≤ 1	4.9	150-170	—	—	—	≤ 1.0	43	—
Brij 76	Solid	≤ 1	12.4	75-90	—	—	—	≤ 3.0	38	—
Brij 78	Solid	≤ 1	15.3	45-60	—	—	—	≤ 3.0	38	—
Brij 93	—	≤ 1	4.9	160-180	—	—	—	≤ 1.0	10	—
Brij 97	—	≤ 1	12.4	80-95	—	—	—	≤ 3.0	16	—
Brij 99	—	≤ 1	15.3	50-65	—	—	—	≤ 3.0	33	—
Cremophor A6	—	≤ 1	10-12	115-135	≤ 1	≤ 3	0.896-0.906 at 60°C	≤ 1.0	41-43	—
Cremophor A11	—	≤ 1	12-14	70-80	≤ 1	≤ 1	0.964-0.968 at 60°C	≤ 1.0	34-36	—
Cremophor A25	—	≤ 1	15-17	35-45	≤ 1	≤ 3	1.020-1.028 at 60°C	≤ 1.0	44-46	—
Ethosperse 1A4	—	≤ 2	—	145-160	—	—	0.95	≤ 0.5	—	—
Ethosperse 1A12	—	≤ 2	—	72-82	—	—	1.10	≤ 1.0	—	—
Ethosperse TDA6	—	≤ 1	—	118-133	—	—	0.98	≤ 1.0	—	—
Ethosperse S120	—	≤ 0.5	—	385-430	—	—	1.16	≤ 1.0	—	—
Ethosperse G26	—	≤ 2	—	133-142	—	—	1.12 at 38°C	≤ 0.5	—	—
Ethylan D252	Liquid	—	5.6	—	—	—	0.903	≤ 0.5	5	Insoluble
Ethylan 253	Liquid	—	7.8	—	—	—	0.930	≤ 0.5	3	Insoluble
Ethylan 254	Liquid	—	9.8	—	—	—	0.948	≤ 3.0	5	Insoluble
Ethylan 256	Liquid	—	11.4	—	—	—	0.972	≤ 0.5	15	43
Ethylan 257	Liquid	—	12.2	—	—	—	0.974 at 40°C	≤ 0.5	21	49
Ethylan 2512	Solid	—	14.2	—	—	—	1.001	≤ 0.5	29	92
Ethylan 2560	Solid	—	18.6	—	—	—	—	≤ 0.5	45	> 100
Plurafac RA20	—	—	—	69-78	—	0.9965	≤ 0.1	4	—	
Plurafac RA30	—	—	—	85-95	—	—	0.976	≤ 0.1	-6	—
Plurafac RA40	—	—	—	65-75	—	—	0.978	≤ 0.2	-27	—
Plurafac RA340	—	—	—	73	—	—	0.977	—	-23	—
Renex 30	Cloudy liquid	≤ 1	14.5	75-85	—	—	1.0	≤ 3.0	14	18.4
Renex 31	—	≤ 1	15.4	60-74	—	—	1.0	≤ 3.0	16	99
Renex 36	—	≤ 1	11.4	118-133	—	—	1.0	≤ 1.0	—	< 32
Texofor A1P	Solid	—	16.2	—	—	—	1.025 at 60°C	—	40	> 100
Texofor AP	—	—	—	—	—	—	0.875	—	31	Insoluble
Texofor A6	Solid	—	—	—	—	—	0.140	—	26	Insoluble
Texofor A10	Solid	—	—	—	—	—	0.970	—	30	75
Texofor A14	Solid	—	—	—	—	—	0.995	—	35	100
Texofor A30	Solid	—	—	—	—	—	1.035	—	43	-> 100
Texofor A45	Solid	—	—	—	—	—	1.055	—	47	> 100
Texofor A60	Solid	—	—	—	—	—	1.065	—	48	> 100
Volpo 10	Hazy liquid	< 2	—	79-91	31-37	—	—	< 1.0	—	> 55
Volpo 20	Soft solid	< 2	—	50-58	18-25	—	—	< 1.0	—	> 100
Volpo S-2	Soft solid	< 1	—	150-170	—	—	—	< 1.0	—	—
Volpo S-10	Soft solid	< 1	—	75-90	—	—	—	< 3	—	—
Volpo S-120	Waxy solid	< 1	—	45-60	—	—	—	< 3	—	—

Table III: Typical properties of selected commercially available grades of polyoxyethylene alkyl ethers.

Name	Critical micelle concentration (%)	Surface tension of aqueous solution at 20°C (mN/m) (0.05%)	(0.1%)	(0.2%)	Dynamic viscosity at 25°C or pour point (mPa s)	Refractive index at 60°C	Solubility Ethanol	Fixed oils	Propylene glycol	Water
Brij 30	—	—	—	—	30	—	S	S	S	I
Brij 35	0.013	—	—	—	—	—	S	I	S	S
Brij 52	—	—	—	—	—	—	S	S	I	I
Brij 56	—	—	—	—	—	—	S	I	I	I
Brij 58	—	—	—	—	—	—	S	S	I	S
Brij 72	—	—	—	—	—	—	S	I	S	I
Brij 76	—	—	—	—	—	—	S	I	I	I
Brij 78	—	—	—	—	30	—	S	S	S	I
Brij 93	—	—	—	—	100	—	S	I	I	S
Brij 97	—	—	—	—	—	—	S	I	S	S
Brij 99	—	—	—	—	—	1.4420-1.4424	S	I	—	S
Cremophor A6	—	—	—	—	—	1.4464-1.4474	S	I	—	S
Cremophor A11	—	—	—	—	—	1.4512-1.4520	S	I	—	S
Cremophor A25	—	—	—	—	30	—	S	S	—	S
Ethosperse IA4	—	—	—	—	1000	—	S	SH	—	S
Ethosperse IA12	—	—	—	—	80	—	S	I	—	D
Ethosperse TDA6	—	—	—	—	460	—	S	I	—	S
Ethosperse S120	—	—	—	—	150 at 38°C	—	S	I	—	S
Ethosperse G26	—	—	—	—	—	—	—	—	—	I
Ethylan D252	—	—	—	—	—	—	—	—	—	I
Ethylan 253	—	—	—	—	—	—	—	—	—	I
Ethylan 254	—	—	—	—	—	—	—	—	—	S
Ethylan 256	—	—	—	—	—	—	—	—	—	S
Ethylan 257	—	—	—	—	—	—	—	—	—	S
Ethylan 2512	—	—	—	—	—	—	—	—	—	S
Ethylan 2560	—	—	—	—	—	—	—	—	—	—
Plurafac RA20	—	—	30.7	—	—	—	—	—	—	—
Plurafac RA30	—	—	28.6	—	—	—	—	—	—	—
Plurafac RA40	—	—	30.3	—	—	—	—	—	—	—
Plurafac RA340	—	—	30.5	—	—	—	—	—	—	—
Renex 30	—	—	—	—	60	—	S	I	—	S
Renex 31	—	—	—	—	130	—	S	I	—	S
Renex 36	—	—	—	—	80	—	S	I	—	D
Texofor A1P	0.006	42.9	—	42.3	—	—	S	—	—	S
Texofor AP	—	—	—	—	—	—	S	—	—	I
Texofor A6	—	—	—	—	—	—	S	—	—	I
Texofor A10	0.004	36.5	—	36.7	—	—	S	—	—	S
Texofor A14	—	36.9	—	36.6	—	—	S	—	—	S
Texofor A30	0.003	46.0	—	46.0	—	—	S	—	—	S
Texofor A45	0.004	47.5	—	47.0	—	—	S	—	—	S
Texofor A60	0.003	48.3	—	48.3	—	—	S	—	—	S

Key: S = Soluble; I = Insoluble; D = Dispersible; SH = Soluble on heating.

Suppliers: ICI Surfactants (*Brij*).

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22. Authors

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